REMARKS

Claims 1-8, 11, 13-19, and 67 are pending in the present application. The Examiner rejected claim 67 under 35 USC Section 112, first and second paragraph. The Examiner rejected claims 1-5, 7, 8, 11, 13, 15, 16, 19, and 67 under 35 USC Section 102(b) as being anticipated by WO 96/22384 (Lemke). The Examiner rejected claims 6, 14, 17, and 18 under 35 USC 103 as being obvious over WO 96/22384 (Lemke) in view of Barth et al.

Claim 67 has been amended. Care has been taken so that no new matter has been added.

Accompanying this Amendment dated July 15, 2004, Applicants submit an Affidavit of Dr. Joseph A. Francisco. Applicants respectfully request that the Examiner consider the Affidavit in conjunction with this Amendment.

Accompanying this Amendment dated July 15, 2004, Applicants submit a Fourth Supplemental Information Disclosure Statement. Applicants respectfully request that the Examiner sign and return a copy of the Statement.

Accompanying the Amendment under 37 C.F.R. § 1.111 dated October 2, 2003, Applicants submitted a Third Supplemental Information Disclosure Statement. Applicants respectfully request that the Examiner sign and return a copy of that Statement.

1. Claim Rejections under 35 USC Section 112

The Examiner rejected claim 67 under 35 USC Section 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Examiner alleges that claim 67 is confusing because it recites that cells are added "in the presence of only RPMI...". Without acquiescing to this rejection, and for purposes of clarity, Applicants have amended claim 67 to remove the recitation of "only."

In the Advisory Action dated April 1, 2004, the Examiner alleges that it is unclear with what the "comparison step" is being compared. Applicants respectfully assert that the comparison is clearly described in claim 67 following "wherein" as "the antibody has a cytostatic or cytotoxic effect on the Hodgkin's

Disease cell line if the cells of the Hodgkin's Disease cell culture have reduced ^{3}H-thymidine incorporation *compared to* cells of the same Hodgkin's Disease cell line cultured under the same conditions but not contacted with the antibody." (emphasis added).

For reasons unrelated to patentability and solely for clarity, Applicants have amended the second recitation of (C) in claim 67 to (E).

The Examiner rejected claim 67 for allegedly lacking sufficient antecedent basis for "the well" in lines 12-13 of the claim. Applicants respectfully direct the Examiner's attention to line 9 of claim 67 wherein proper antecedent basis is provided by the recitation of "a well."

The Examiner rejected claim 67 under 35 USC Section 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner alleges that claim 67 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of filing the application, had possession of the claimed inventions. The Examiner alleges that the application does not support a "Hodgkin's disease cell line is added to a well in presence of only RPMI with 10% or 20% FBS. The specification at page 50 at lines 19-24 does not say that Hodgkin's disease cell line is grown in RPMI with 10% or 20% FBS." Without acquiescing to this rejection, and for purposes of clarity, the Applicants have amended claim 67 to remove the recitation of "10% fetal bovine serum or." Applicants respectfully assert that all rejections under 35 USC 112 have been successfully overcome.

2. Claim Rejections under 35 USC Section 102

The Examiner rejected claims 1-5, 7, 8, 11, 13, 15, 16, 19, and 67 under 35 USC Section 102(b) as allegedly being anticipated by WO 96/22384 ("Lemke"). Applicants traverse this rejection.

Applicants respectfully assert that, contrary to the Examiner's assertion in the Advisory Action of April 1, 2004, Applicants are not required to provide evidence that the claimed invention does not "posses the functional characteristics disclosed in claim 1 of Lemke." Advisory Action, Continuation

Sheet, line 21. Rather, the Examiner has a duty to establish a *prima facie* case of anticipation. For a reference to anticipate a claim, it must *clearly and unequivocally disclose*, not merely suggest each and every element of the claimed invention as arranged in the claims. *See Idacon v. Central Forrest Products, 3 USPQ 2d 1079, 1083* (emphasis added). Applicants assert that Lemke does not teach "[a] method for the treatment of Hodgkin's Disease ... comprising administering ..." an antibody that "...exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent ..." as claimed in claim 1. Therefore, "the claimed antibody is different from those taught by Lemke." Advisory Action, Continuation Sheet, lines 24-25.

As recited in the MPEP, paragraph 706.02(IV) " ...for anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either expliciedly or impliciedly." "A claim is anticipated only if each and every element ... is found in a single prior art reference." MPEP 2131. A reference must be cited for what it fairly teaches. *In re Burkel*, 201 U.S.P.Q. 67 (C.C.P.A. 1979). The Examiner must first meet her initial burden. It is the Examiner's duty to show each and every element of a claim. It is not the Applicant's duty to refute that a claimed invention does not posses certain functional characteristics. Applicants respectfully assert that the Examiner has not established a *prima facie* case of anticipation. The Examiner has not shown where Lemke teaches an antibody that "exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent ..." as claimed in claim 1.

Lemke teaches anti-CD30 antibodies that do not promote the release of CD30 from a cell surface, but instead inhibit the release of soluble CD30, and are specific for Hodgkin and Sternberg-Reed cells, making those antibodies potentially *useful in the delivery of toxins* to Hodgkin's disease cells. *See*, page 2, ¶ 3 (emphasis added). Further, Lemke discloses as an object of the invention, "to provide new CD30-specific antibodies which do not promote the release of the sCD30, but inhibit the formation of the sCD30 instead and thus would

possibly allow the *formation of powerful* immunotoxins." Lemke, page 2, lines 19-21. Lemke discloses Ki-4 as an exemplary antibody. See Lemke, at least page 2, lines 29-31, and page 5, lines 7-9 ("especially Ki-4").

Lemke does not teach an antibody that "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent." Applicants would like to remind the Examiner that not all naked antibodies have cytostatic or cytotoxic properties. See Affidavit of Dr. Joseph A. Francisco attached hereto. There are no studies, examples, disclosure, or data in Lemke that show an antibody not linked to a toxin having any kind of cytostatic or cytotoxic effect on a Hodgkin's Disease cell line. Additionally, there is no disclosure by Lemke in the application directed to *any* studies, data, or examples of an antibody linked to an immunotoxin that has a cytotoxic or cytostatic effect on a Hodgkin's Disease cell line. Rather, all that Lemke can "fairly teach" (*In re Burkel*, 201 U.S.P.Q. 67 (C.C.P.A. 1979)) is an antibody that does not promote the release of soluble CD30 from a cell surface and which is specific for Hodgkin's and Sternberg-Reed cells. There is no disclosure as to the activity of the antibodies, either "naked" or conjugated to an immunotoxin.

Applicants respectfully assert that the Examiner is reading into Lemke that which is not there. The Examiner recites that "Lemke teaches treatment of Hodgkin's disease using a generic anti-CD [sic] antibody (without any toxin attached) that releases soluble CD30 from Hodgkin's disease cells to an amount of less than 10% at the abstract and claims 13 and 14." Applicants respectfully assert that the Examiner has not shown where Lemke discloses cytotoxic or cytostatic effects. Applicants will address claims 1, 4, 13 and 14 of Lemke immediately below.

Claim 1 of Lemke is a composition claim, not a method claim, directed to a naked antibody. Specifically, claim 1 of Lemke recites:

An antibody which binds to the CD30 antigen and

a) releases sCD30 from Hodgkins disease cells to an amount of, or less than, 10% referred to the release found without an addition of antibody;
b) does not bind to B cell non Hodgkin's lymphomas or plasma cells to a considerable extent.

Applicants respectfully assert, upon careful reading of claim 1 of Lemke and not reading into claim 1 of Lemke that which is not present, that claim 1 of Lemke is directed towards a naked antibody with the properties recited in (a) (generally shedding) and (b) (generally binding) and makes no mention of treatment.

Claim 4 of Lemke is to the naked antibody of claim 1 linked to a toxin. Claim 4 is a composition claim, not a method claim. Claim 4 does not recite the naked antibody of claim 1 linked to a toxin for the treatment of Hodgkin's disease.

Claim 13 recites that the naked antibody of claim 1 and/or the linked antibody of claim 4 can be used in "the *manufacturing of a therapeutic agent*" for the treatment of Hodgkin's disease. It does not say that it can be used AS the treatment. Further, claim 13 says nothing about how the antibody of claim 1 to 7 could be used in the manufacturing of a therapeutic agent for the treatment of Hodgkin's disease.

Claim 14 is directed towards *a pharmaceutical composition* containing the naked antibody or linked antibody. Claim 14 of Lemke is not directed towards treatment of Hodgkin's disease using the antibody of claim 1 to 7. Contrary to the Examiner's assertion in the Advisory Action, Applicants respectfully assert that nowhere does Lemke mention cytostatic or cytostatic effects of the naked antibody. Therefore, Lemke cannot anticipate claim 1, or any claims dependant therefrom, of the instant application.

The Examiner invited Applicants to present "scientific data" to the office that "the various antibodies claimed in claim 1 of the art of record does not have the activity recited in the instant claims in order to obviate this rejection." Office Action of January 1, 2004, page 4, lines 6-9. Applicants provided the Examiner with an article by Engert *et al.* Further, Applicants provide the Examiner with an article by Schnell *et al.*, "Development of New Ricin A-Chain Immunotoxins with Potent Anti-Tumor Effects Against Human Hodgkin Cells *in Vitro* and

Disseminated Hodgkin Tumors in SCID Mice Using High-Affinity Monoclonal Antibodies Directed Against the CD30 Antigen," *Int. J. Cancer* 63:238-244 (1995) (Schnell[1]). Additionally, Applicants provide the Examiner with the Affidavit of Dr. Joseph Francisco. These documents re-enforce that it was known that neither Ki-4 nor Ber-H2 have the function of "exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent" as claimed in claim 1. Schnell *et al* (the Examiner may note that Dr. Hilmar Lemke is an author on this publication) describe experiments using a Ki-4 immunotoxin (IT) and naked (native) Ki-4 antibody. On page 241, left column, lines 29-31, Schnell *et al* state that the cytotoxicity of the immunotoxins was specific yet the naïve antibodies *were not toxic*. Additionally, on page 241, right column, lines 10-13, Schnell *et al* state that treatment with Ki-4 did not induce complete remission. As recited in the Affidavit of Dr. Francisco, upon reading Schnell *et al*, one of skill in the art would know that Ki-4 does not exert cytostatic or cytostatic effects.

Lemke discloses Ber-H2 and Ki-4 as Cluster A antibodies. Ber-H2 and Ki-4 are both "antibodies claimed in claim 1 of the art of record." Evidence shows that antibodies of Lemke's Cluster A (including Ki-4 and Ber-H2) do not have intrinsic cytotoxic or cytostatic effects. The Examiner is invited to review Engert *et al.*, "Evaluation of Ricin A Chain-containing Immunotoxins Directed Against the CD30 Antigen as Potential Reagents for the Treatment of Hodgkin's Disease," *Cancer Res.* 50:84-88 (1990) ("Engert"[2]). Engert *et al* discloses that Ber-H2, when not conjugated to a toxin, failed to show any cytotoxicity towards Hodgkin's cell line L540 (page 86, right column, ¶ 2: "The cytotoxic effect of all of the immunotoxins was specific since the native antibodies . . . were not toxic at 10^{-6} M."). That is, Ber-H2 does not exert "the cytostatic or cytotoxic effect on the

[1] Cited by Applicants in the Fourth Supplemental Information Disclosure Statement dated July 15, 2004 as reference BR. Applicants do not admit or make any representation that Schnell is prior art.

[2] Cited by Applicants in the Information Disclosure Statement filed June 4, 2001 as reference AJ.

Hodgkin's Disease cell line...in the absence of cells other than cells of said Hodgkin's Disease cell line" as recited in claim 1. Therefore, as requested by the Examiner, Applicants have shown scientific data that "the various antibodies claimed in claim 1 of the art of record *does not have the activity recited in the instant claims* in order to obviate this rejection." Office Action of January 1, 2004, page 4, lines 6-9.

Without acquiescing that the Examiner has made a *prima facie* case of anticipation, the Applicants assert that Lemke is inoperative to teach or suggest a naked antibody that has cytostatic or cytotoxic properties. See MPEP 2121. In accordance with MPEP 716.07, the Applicants submit herewith the Affidavit of Joseph A. Francisco to attack the operability of Lemke.

As Lemke fails to teach an antibody that "exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line", Lemke cannot render claim 1, or any claim dependant there from, anticipated under 35 U.S.C. § 102(b).

Lemke also does not anticipate claim 8. Lemke does not teach a protein which "competes for binding to CD30 with monoclonal antibody AC10 or HeFi-1" as claimed in claim 8. Lemke, as noted above, teaches that antibodies in Cluster A are useful for the treatment of Hodgkin's disease, and that Cluster A antibodies, such as Ki-4, do not compete with Cluster C antibodies, such as HeFi-1 or AC10, for binding to CD30. Lemke teaches that Ki-4, a member of Cluster A, fails to compete with HeFi-1 in Group C. (*See* Table II, page 21). Lemke fails to teach or suggest an antibody that "competes for binding to CD30 with monoclonal antibody AC10 or HeFi-1". Lemke discloses that Ki-4 (cluster A) does not compete for binding with AC10 (Cluster C). See Lemke, page 18, lines 12-14. Lemke additionally discloses that HeFi-1 enhanced the release of sCD30. See, page 18, lines 24-26. Therefore, even Lemke distinguishes the claimed antibodies from antibodies that decrease the solubility of CD30. Further, as discussed above, Lemke fails to teach an antibody that "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line" as claimed in claim 8. As Lemke fails to teach an antibody that "exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line" and "competes for binding to CD30 with

monoclonal antibody AC10 or HeFi-1," Lemke cannot render claim 8, or any claim dependant there from, anticipated under 35 U.S.C. § 102(b).

Lemke also does not anticipate claim 11. Lemke does not teach an antibody which "comprises an amino acid sequence that has at least 95% identity to SEQ ID NO:2" as claimed in claim 11. Lemke teaches antibodies in Cluster A are useful for the treatment of Hodgkin's disease. AC10 falls into Cluster C of Lemke. SEQ ID NO:2 is directed towards the amino acid heavy chain variable region of AC10. (See, page 9, Table 1). Therefore, Lemke fails to teach for therapeutic use antibodies that "comprises an amino acid sequence that has at least 95% identity to SEQ ID NO:2", and does not anticipate claim 11.

Lemke does not anticipate claim 67. Lemke does not teach the method described in claim 67. Therefore, Lemke does not anticipate claim 67.

Because Lemke fails to anticipate claims 1, 8, 11, or 67, Lemke cannot anticipate any claims depending therefrom. Therefore, Applicants respectfully request the Examiner withdraw the rejection of these claims.

3. The Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 6, 14, 17, and 18 under 35 USC 103 as being unpatenable over WO 96/22384 (Lemke) as applied to claims 1-5, 7, 8, 11, 13, 15, 16, and 19, and further in view of Barth et al. Applicants respectfully traverse this rejection.

Applicants submit that the subject matter of these claims is not obvious over this combination of publications because the Examiner has not provided the proper motivation for making this combination, as required by MPEP 2142-2144.02. Particularly, the Applicants assert that the Examiner has failed to make a *prima facie case* of obviousness. As recited in MPEP paragraph 2142 "[t]he examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness."

As discussed in the remarks above, Lemke fails to teach or suggest an antibody that "exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line...in the absence of cells other than cells of said Hodgkin's Disease cell

line" as claimed in claim 1. Barth *el at* teach an immunotoxin. Barth *et al* do not teach or suggest the deficiency of Lemke.

Therefore, since Barth *et al* also do not teach or suggest the deficiencies of Lemke, neither Lemke alone nor in combination with Barth *et al* can render claims 1 or 8, or any claims dependant therefrom, obvious.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicants respectfully request that the Examiner call the undersigned attorney at (425) 527-4122 if any questions or issues remain.

Respectfully submitted,

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